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Review

Practical aspects of vaccination of poultry against avian influenza virus

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ABSTRACT

Although little has changed in vaccine technology for avian influenza virus (AIV) in the past 20 years, the approach to vaccination of poultry (chickens, turkeys and ducks) for avian influenza has evolved as highly pathogenic AIV has become endemic in several regions of the world. Vaccination for low pathogenicity AIV is also becoming routine in regions where there is a high level of field challenge. In contrast, some countries will not use vaccination at all and some will only use it on an emergency basis during eradication efforts (i.e. stamping-out). There are pros and cons to each approach and, since every outbreak situation is different, no one method will work equally well in all situations. Numerous practical aspects must be considered when developing an AIV control program with vaccination as a component, such as: (1) the goals of vaccination must be defined; (2) the population to be vaccinated must be clearly identified; (3) there must be a plan to obtain and administer good quality vaccine in a timely manner and to achieve adequate coverage with the available resources; (4) risk factors for vaccine failure should be mitigated as much as possible; and, most importantly, (5) biosecurity must be maintained as much as possible, if not enhanced, during the vaccination period.

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Introduction

Avian influenza (AI) is among the most economically important diseases affecting poultry. Although much attention tends to be focused on the potential public health aspects of AI virus (AIV) infections, the impact on animal health is substantial. Control of AI has historically focused on prevention of infection, then eradication, when outbreaks occur in domestic poultry, especially with the highly pathogenic (HP) form of AI (HPAI). However, the use of vaccines in poultry has increased during the past two decades, in part because of the increase in the number of countries with endemic AI. Adding to the complexity of AI control, the use of vaccines against AI is under government control in most countries. Therefore the implementation and approach to AI vaccination can vary greatly between neighboring countries that have the same biological threat from AI, but different policies toward its control.

Vaccines against AI virus (AIV) have been available for some time and are generally safe and efficacious when used properly (OFFLU, 2013). Disincentives to vaccination include the high labor costs of vaccination in some countries and trade embargoes. AIVs of the H5 and H7 subtypes in domestic poultry are reportable to the World Organisation for Animal Health (OIE, 2012); therefore, numerous countries find it favorable to prevent infection and, if that fails, then to immediately eradicate or stamp out the virus without vaccinating.

Reluctance to vaccinate also comes from the belief that vaccines could potentiate spread of HPAI virus (HPAIV) because they can mask infection, so that poultry appear to be free of infection, but could shed virus into the environment, thus perpetuating the disease. There is evidence that the use of vaccines to control HPAIV in numerous outbreaks has not led to the virus becoming endemic (Ellis et al., 2004; Swayne et al., 2011). Also, shortcomings in biosecurity are a major contributing factor to poor control of AIV (Peyre et al., 2009b), particularly when vaccination was implemented after the virus was already endemic in a region (Swayne, 2012). If flocks are not vaccinated against low pathogenicity (LP) H5 and H7 AIV, silent infection with LPAIV could be established, increasing the chance of the virus mutating to HPAIV (Halvorson, 2002). When vaccine use has been prohibited, farmers will sometimes expose pullets to AIV to prevent later production losses (Halvorson, 2002).

Use of vaccines for a limited time during eradication to prevent the spread of the AIV within specific groups of animals represents one of the most successful uses of vaccines for control of AI (Naeem and Siddique, 2006; Swayne, 2012). In poultry producing areas where

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AIV has become endemic, vaccine may be used routinely in at-risk populations (Domenech et al., 2009; Sims, 2012).

There are pros and cons of each approach, and each has strong advocates. In view of different poultry industry structures, differences in resource availability and other variables, there is no single approach that will work optimally for every AI outbreak. However, good quality vaccines are a critical tool for minimizing losses and help to reduce the spread of the virus when used properly.

Avian influenza virus in poultry

Clinical disease

The clinical disease associated with AI in poultry has been reviewed extensively (Swayne and Pantin-Jackwood, 2008; Capua and Alexander, 2009; OIE, 2012; Swayne and Spackman, 2013; Swayne et al., 2013). AI presents with two distinct pathotypes; HPAIV causes systemic infection and LPAIV primarily causes respiratory infection. In gallinaceous birds (e.g. chickens, turkeys and quail), HPAI is characterized by rapid, high mortality and, depending on the strain, birds may present with severe lethargy, neurological signs, ecchymotic hemorrhages on the shanks, swelling and cyanosis of the comb and wattles, green diarrhea and/or heavy mucous exudate in the upper respiratory tract (Swayne and Spackman, 2013; Swayne et al., 2013).

Only some strains of the H5 and H7 subtypes of AIV have been recognized as HP. The HP form evolves from the LP form when the virus persists in a population of gallinaceous hosts. Viruses which are HP for gallinaceous birds usually do not cause morbidity or mortality in wild or domestic waterfowl, although there are some specific strains of H5N1 HPAIV that can cause disease and death in domestic ducks, e.g. Pekin ducks (Pantin-Jackwood and Suarez, 2013). Importantly, wild birds carry the LP form, except in rare situations where they become infected with HPAIV from domestic poultry.

Most AIVs are LPAIVs. The LP form can be caused by any of the 16 HA subtypes of AIV. Disease from LPAIV is typically mild and may be subclinical in domestic avian species (e.g. chickens, ducks, turkeys, geese and quail) when uncomplicated. When disease does occur, upper respiratory signs with swollen heads and lacrimation, and mild lethargy, are common (Swayne and Spackman, 2013; Swayne et al., 2013). One of the first signs of LPAI in the field is a decrease in feed and water consumption, due to reluctance to move. Transient, and sometimes severe, drops in egg production are also common (Swayne and Spackman, 2013; Swayne et al., 2013). One of the most important impacts of LPAI is that it can cause substantial losses in egg production, particularly in turkey breeders. Birds will often recover fully from the respiratory disease if they are otherwise healthy, although some strains have caused severe losses, e.g. A/chicken/AL/1975 H4N1 and some H9N2 strains (Brugh, 1992; Iqbal et al., 2013).

Risk factors for infection and disease

Risk factors for exposure of domestic poultry to AIV are summarized in Table 1 and risk factors affecting the severity of disease for chickens and turkeys are shown in Fig. 1. These host and management factors typically only affect the severity of LPAI, because HPAI is so severe that many otherwise healthy chickens and turkeys will die from the disease.

Wild aquatic birds are the natural reservoirs of AIV, which causes subclinical infection and replicates preferentially in the intestinal tract of waterfowl. The initial introduction of AIV into domestic birds frequently occurs by contact with wild birds or their excreta; typically when domestic birds have access to the outside or are provided with untreated water from nearby surface water sources where waterfowl gather. When range rearing of turkeys was phased out from around 1997, the incidence of AI in turkeys in Minnesota, USA, decreased. Conversely, animal welfare concerns have driven poultry production outside in Europe, where the incidence of AI has increased (Bonfanti et al., 2014).

Table 1
Risk factors for severity of avian influenza in poultry.

Risk factor	Causes
Season	Houses closed in cold weather have poorer air quality which can damage the respiratory epithelium and cause inflammation Cold or heat stress weakens birds and can cause immunosuppression
High ammonia levels in the house	High ammonia levels will damage the respiratory epithelium and cause inflammation
Prior infection with immunosuppressive agents	The immune system is too impaired to control infection
Prior or concomitant infection with other respiratory disease agents	Can damage the respiratory epithelium and cause inflammation
Age of birds	Very young birds and hens producing eggs may be more susceptible to infection and disease

Rearing multiple avian species together, especially mixing waterfowl and gallinaceous birds, will also increase risk of AI. Once the virus is in poultry, proximity to infected flocks and even to roads on which birds or excreta from infected flocks are moved increases the risk of infection (Akey, 2003). Population density is important to propagating the virus and areas of intensive poultry production or multiage operations have increased risk.

Consideration of these factors will influence which populations to vaccinate and the strategies adopted to optimize the efficacy of vaccination. Chickens exposed to infectious bursal disease virus (IBDV), an immunosuppressive virus, will not respond as well to AI vaccination as unexposed chickens (E. Spackman, unpublished data). In multi-age operations, pullets or incoming younger birds may need to be vaccinated if the older birds on the premise are infected.

Historical use of avian influenza vaccines in poultry

Numerous recent reviews have covered the history of AIV vaccine use in detail (Naeem and Siddique, 2006; Brown et al., 2007; Seck et al., 2007; Swayne and Kapczynski, 2008; Peyre et al., 2009a; Swayne et al., 2011). The earliest vaccines for AIV date back to the late 1920s and 1930s for HPAIV or 'fowl plague' (Todd, 1928; Purchase, 1930). More recently, worldwide vaccination of chickens and turkeys is by far most common for the H5 (HP and LP), H7 (HP and LP) and H9 (LP) AIV subtypes. Vaccination against H5 may

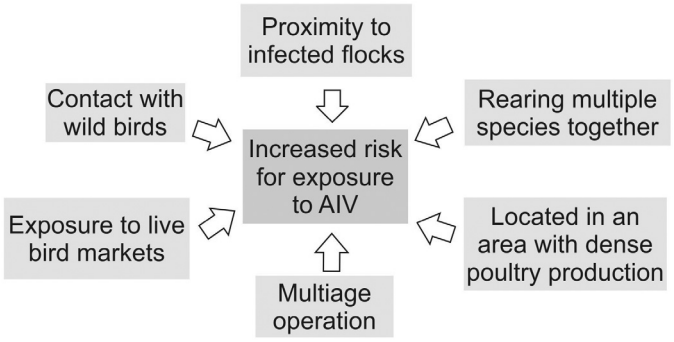

Fig. 1. Numerous factors increase the risk that a given population of domestic birds would be exposed to avian influenza virus (AIV).

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be for HPAIV (currently used in Egypt, Vietnam, China and Indonesia) or LPAIV (Mexico). Remarkably, 99% of all AIV vaccine use in poultry by dose has been in four countries (China, Indonesia, Vietnam and Egypt) for H5N1 HPAIV (Swayne et al., 2011).

Turkey breeders in the USA and Canada may be vaccinated against H3 and H1 swine influenza, because pigs and turkeys are frequently reared in proximity to each other and swine influenza will cause substantial drops in egg production in turkeys. Vaccination for other LPAIVs of various subtypes (e.g. H2, H4 and H10) has been used temporarily in turkey breeders to prevent decreases in egg production when there is a known risk for specific flocks (Swayne et al., 2011). Controlled marketing has also been employed as an additional measure to reduce the spread of virus, e.g. birds are not moved to slaughter until it can be demonstrated that they are no longer shedding virus (or at least until the risk of shedding is reduced) and even then are processed as the last flock of the day, (Halvorson, 2009). Vaccination for H6 LPAIV has been used in Germany and in ostrich breeders in South Africa (Swayne et al., 2011).

Vaccination against H9 LPAIV has been used in the Middle East and Asia. Israel and Pakistan, among other countries, have used H9 vaccines to control recurrent outbreaks in chickens and turkeys, since the field impact of H9, although LP, can be severe (Naeem and Siddique, 2006; Perk et al., 2009). The impact of H9 LPAIV is, in part, because it exacerbates disease and production losses caused by other common respiratory pathogens (Nili and Asasi, 2003; Roussan et al., 2008). Vaccination of chickens against H7 HPAIV has been used successfully in Pakistan to aid eradication efforts (Naeem and Siddique, 2006; Naeem et al., 2007).

Vaccination of chickens against AIV in Mexico is a unique case. H5N2 HPAIV emerged in poultry in Mexico in 1994 and was eradicated by 1995; however, the LP form of the same virus strain has not been eradicated and continues to circulate in many of the poultry producing states of Mexico (Senne, 2007; Pasick et al., 2012). In addition to long term vaccination against H5 LPAIV, vaccination against H7N3 HPAIV, which caused outbreaks in chickens in 2012 and 2013, has also been implemented.

Domestic ducks generally are only vaccinated against H5N1 HPAIV in Asia. Although a limited number of H5N1 HPAIV strains can cause morbidity and mortality in domestic ducks, the impact of this strain on duck production is less severe than on gallinaceous birds, so vaccination of ducks is typically employed to reduce the risk for human beings and chickens by decreasing the amount of virus excreted (Pantin-Jackwood and Suarez, 2013).

Vaccine technology

Inactivated, oil adjuvanted, whole virus vaccines are the most common vaccines available for AIV and account for 95.5% of AIV vaccine usage in poultry (Swayne et al., 2011). Although these vaccines are relatively simple to produce, they are expensive to administer, because they must be applied intramuscularly or subcutaneously.

Vectored vaccines containing the AIV hemagglutinin (HA) gene in a viral vector have been used in the field on a more limited basis and are not licensed in as many countries as the inactivated vaccines. Fowl pox virus (FPV), herpesvirus of turkeys (HVT) and nonvirulent avian paramyxovirus type 1 (APMV-1) have all been utilized as vectors for AIV vaccines in the field (Swayne et al., 1997; Bublot et al., 2006; Qiao et al., 2006; Chen, 2009; Sarfati-Mizrahi et al., 2010). The advantages of vectored vaccines are that some can be administered using automated methods (e.g. HVT injected in ovo; APMV-1 as a spray or in drinking water), or can be given in conjunction with other routine vaccinations (e.g. FPV wing web vaccination). A vaccine using attenuated duck enteritis virus (DEV) as a vector has been developed to control H5N1 HPAI in ducks (Liu et al., 2011).

Vectored vaccines often do not induce long term immunity and, therefore, additional vaccinations with inactivated vaccines are necessary. Also, many require maintenance of the cold chain (HVT vaccines are stored in liquid nitrogen), which increases the cost and complicates the logistics of transport and administration. Finally, if there is any pre-existing immunity to the vector, the vaccination will fail to immunize the bird against AIV. One exception is HVT vectored vaccines delivered in ovo; these are not susceptible to maternal antibodies, but do not induce long term immunity (Li et al., 2011; Rauw et al., 2012). Experimental vaccines with infectious laryngotracheitis virus, adenovirus and *Salmonella enterica* vectors have been reported, but none have been licensed or applied in the field to date (Layton et al., 2009; Park et al., 2009; Pavlova et al., 2009).

Of the vectored vaccines, APMV-1 vectored vaccines have the most potential to induce relevant mucosal immunity, since APMV-1 has similar tissue tropism to AIV. However, APMV-1 is ubiquitous and vaccination against it is widespread; therefore, pre-existing immunity to the vector limits the utility of APMV-1 vectored vaccines.

Infectious vaccines are unlikely to be an option for poultry, since there is a risk of H5 and H7 strains mutating to HP and also a risk of reassortment of other subtypes to more virulent forms. Furthermore, the current trade and regulatory hurdles would be difficult to surmount.

Due to the limitations of current vaccine technology, development of better vaccines is a research priority. Reviews of research and practical needs for AIV vaccines have been reported (OFFLU, 2013; Swayne and Spackman, 2013). Much of the focus on vaccine technology for AIV in the recent literature is directed at producing human vaccines for AIV in the event of a pandemic, not on vaccines for use in poultry. There are no clear 'game-changing' technologies (e.g. adjuvants, vaccine platforms, delivery systems) on the horizon for AIV vaccination of poultry. Practicality, cost and licensing are barriers to adoption for many of the current experimental approaches; therefore, it is evident that the current vaccines will be in use for some time.

Vaccine quality/potency

Vaccine quality (e.g. potency) varies among vaccines and affects efficacy. Currently, the only reliable way to evaluate how a vaccine will perform against a specific challenge virus is to conduct in vivo challenge trials in the target species, noting that turkeys, ducks and geese may not respond in the same way as chickens (Tumpey et al., 2004; Eggert and Swayne, 2010). In vivo vaccination-challenge trials are time consuming (a minimum of 5 weeks) and expensive, particularly when working with HPAIV and/or strains that are potentially infectious to human beings, since these require increased biosafety and biosecurity. There are no universally accepted methods for evaluating vaccines in vivo: bird age, species/breed, number of immunizations, time between immunization and challenge, challenge virus dose and strain can vary and will affect vaccine performance.

Vaccines usually perform better in the laboratory than in the field due to the cleaner conditions and often because birds used experimentally are specific pathogen free and have not been exposed to other respiratory or immunosuppressive agents. Although there is not a good correlation between antigen content and protection with heterologous strains (Swayne et al., 1999), there is a need to establish standards for the minimum amount of antigen in a vaccine and to develop methods to directly evaluate the antigenic content of vaccines so that vaccine batches can be evaluated without challenge studies.

The initial selection of an HA to use as a vaccine antigen is based on the protein identity between the prospective vaccine and the field strain. Data on the minimum identity needed for protection are complex, since a good immunogen can 'overcome' antigenic dif-

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ferences and not all amino acid changes affect epitopes. Antigenic cartography, which uses hemagglutination inhibition (HI) or virus neutralization (VN) data to map the distance between antigens, has been proposed as a method for antigen selection (Smith et al., 2004; Cai et al., 2010, 2011; Fouchier and Smith, 2010). However, in the relatively few challenge studies that have been conducted to assess this approach, there is no clear relationship between antigenic distance and protection (Abbas et al., 2011; Spackman et al., 2014; E. Spackman, unpublished data).

Serology is frequently used to evaluate the response of poultry to vaccines in the field and may be used for AI vaccines. Evaluation of serological responses can be complicated when vaccinated birds have been naturally exposed to AIV, including a range of subtypes. Numerous commercial ELISAs are available for detection of antibodies against AIV, but not all are quantitative and the minimum protective ELISA antibody levels for AI virus have not been established.

HI is a quantitative serological assay, but is more time consuming and technically demanding than ELISA. HI titers of at least 5–6 $\log_2$ against the challenge virus will frequently correspond to adequate protection against disease and death (van der Goot et al., 2005; Kumar et al., 2007; Abbas et al., 2011; Grund et al., 2011; Spackman et al., 2014). However, birds with low or absent HI antibodies to the vaccine may still be protected from morbidity and mortality (Abbas et al., 2011; Cha et al., 2013; Spackman et al., 2014). One explanation is that the HI assay does not measure antibodies to the HA fusion domain or another neutralizing epitope (Imai et al., 1998; Fleury et al., 1999).

A third serological test, which typically is not used for vaccine serology, is agar gel immunodiffusion (AGID) (Beard, 1970). Although AGID is inexpensive and easy to use, it is not quantitative, measures immunoglobulin M, is type specific and does not work equally well with all avian species, e.g. AGID does not work consistently with waterfowl sera (Spackman et al., 2009).

Vaccine protection

The HA protein contains the cell receptor binding site and is a neutralizing epitope; as a consequence, it is the primary antigenic determinant of influenza A viruses. HA is the primary target of vaccines, which need to match the HA subtype to be effective (i.e. an H5 vaccine must be used for an H5 challenge strain). Antigenic variation within an HA subtype can also affect vaccine efficacy; therefore, vaccines should be prepared with the closest relative to the field challenge virus. In some cases, the best antigenic match may be an HPAIV; in these situations, the HA may be converted by reverse genetics to a LPAIV for maximum safety, a process which usually does not affect the antigenic structure of the HA. Immunogenicity varies among HA proteins and, in some cases, a highly immunogenic protein will provide better protection than a closer antigenic match (which is why testing vaccines with a relevant challenge virus is critical). The presence of N-linked glycosylation sites might affect immunogenicity (Klenk et al., 2002).

In chickens, strongly immunogenic HA proteins can sometimes overcome antigenic distance within a subtype. For example the A/Hidalgo/232/1994 H5N2 LPAIV strain provided protection against the Asian H5N1 HPAIV for many years, despite an amino acid identity of around 88% in the HA1 with the early isolates (e.g. A/goose/Guandong/1/1996) (Pfeiffer et al., 2010). Eventually, the antigenic structure of the field viruses began to drift and the efficacy of this strain against more recent field viruses was reduced (Abdel-Moneim et al., 2011; Grund et al., 2011; Cha et al., 2013; Leung et al., 2013). Conversely, closely related but poorly immunogenic HA proteins frequently make inadequate vaccines (Naeem and Hussain, 1995; Naeem and Siddique, 2006).

Vaccine efficacy is measured by reducing or eliminating mortality and clinical disease, and reducing the amount of virus excreted, i.e. by at least 2 $\log_{10}$ (Suarez et al., 2006). Although reducing the susceptibility of a population to infection is a key element in vaccine efficacy (Capua et al., 2004), it is rarely measured because of the cost of such experiments. Vaccines are most often selected for their ability to reduce morbidity and mortality, rather than for reduction of virus excretion; however, mortality and morbidity may be reduced even when virus excretion is not substantially reduced. Reduction in virus excretion is crucial for vaccine programs to be successful, since it decreases contamination of the environment and transmission of the virus. However, complete elimination of excretion is difficult to achieve, even in laboratory studies.

Vaccine use in the field

Populations targeted for vaccination

Since the HA subtype of the vaccine must match the subtype of the field virus, preventive vaccination can only be used when there is a known specific threat to a population of poultry, such as proximity of a flock to an outbreak. Due to the cost of vaccine administration, vaccination may not be justified in broiler chickens that have a short lifespan, but may be warranted in longer lived and more valuable birds. In commercial production, these would include table egg layers and breeders (multipliers, grandparents, pedigrees). Vaccination may be feasible in slower growing meat birds, such as the Chinese 'yellow feathered' chicken, which are not marketed until they are ~90 days of age. Other domestic populations that could be vaccinated include birds in zoological collections or aviaries, particularly rare and endangered species.

Another prohibition to vaccination of broilers is that, in many countries, the mandated withdrawal time after vaccination with an inactivated oil-adjuvanted vaccine is longer than the lifespan of the bird. Exceptions, where broilers are vaccinated, are currently Egypt and Mexico, where low labor costs and a high field challenge from endemic HP and LP AIV make vaccination feasible for reducing production losses. A vaccine that could be applied in the hatchery would be beneficial, but would need to overcome the immunological immaturity of chicks at hatch and would still need to be mass applied.

To a more limited extent, vaccination of poultry is also practised in small commercial farms, villages and households in countries with poor biosecurity (Food and Agriculture Organization, FAO, sectors 3 and 4). In these cases, flock health and vaccination records are often poor and, because vaccine coverage is often inadequate in these types of poultry holdings, there are often enough susceptible birds that these populations will serve as reservoirs of the virus and/or as naïve hosts when the virus is re-introduced.

Vaccination of domestic ducks is practised in areas where H5N1 HPAIV is endemic and presents unique challenges, since ducks are almost exclusively reared outside, with minimal confinement, which frequently allows access to other domestic animals. Also, H5N1 HPAIV does not always cause disease or mortality in ducks, so vaccination is not always seen as a priority for duck farmers. The overall effectiveness of vaccination campaigns in ducks has been undermined by the length of the vaccine withdrawal period, rumors concerning adverse reactions, training and payment of vaccinators, lack of vaccines formulated for waterfowl, spoilage of vaccine stocks and rapid turn-over of at-risk populations (van den Berg et al., 2008; Peyre et al., 2009a; Soares Magalhaes et al., 2010). Therefore, vaccinating a sufficient number of ducks to maintain flock immunity (i.e. adequate vaccine coverage) is difficult and represents an obstacle for the control of H5N1 HPAIV (Pantin-Jackwood and Suarez, 2013).

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Practical elements of vaccine use in the field

Trade consequences are an important disincentive for utilization of vaccination as a long-term method for AIV control. Since H5 or H7 subtype AIV is reportable to the OIE, trade can be restricted from countries which vaccinate poultry for AIV, since vaccines can prevent disease, but not infection. Therefore, countries which vaccinate against AIV long term generally do not export as a major part of their markets. For this reason, vaccination probably would not be used widely in countries with substantial export markets, even if the cost of application was low.

During a vaccination program, it is crucial to maintain surveillance for field viruses. Regularly monitoring unvaccinated sentinel birds in a vaccinated flock for virus and/or antibodies is valuable, but requires a method to easily identify sentinel birds so they can be excluded from vaccination and selected for sampling. Sentinel birds are often used with caged layers, since the sentinels can be identified by cage location. In addition, dead birds should be targeted for testing for exposure of a flock to AIV.

An alternative, or even adjunct, system is to use a vaccine compatible with differentiating infected from vaccinated animals (DIVA) (Capua et al., 2003). Various strategies have been developed for DIVA and the technology has numerous pros and cons (Suarez, 2012). The basic concept is to use a vaccine that will not induce antibodies to proteins that will be produced during infection with replicating virus, e.g. when using an H7N3 vaccine for an H7N1 field strain, infected animals will have antibodies against N1, but vaccinated birds will not; instead, they will only have antibodies against N3 (Capua et al., 2003).

Vaccines need to be monitored for efficacy and long term vaccination requires periodic updates of the vaccine seed strain. AIV undergoes antigenic drift and eventually escapes the host immune system, so the efficacy of vaccines is eventually reduced (Lee et al., 2004; Smith et al., 2004; Escorcia et al., 2008; Grund et al., 2011). Although the process is improving in many countries, regulatory structures and commercial vaccine producers generally do not have a system to update AIV vaccines with the same efficiency as the human influenza vaccine production system and ineffective vaccines may be used longer than they should be. This is one of many factors contributing to vaccine failures and adds to the potential for virus spread despite vaccination, since vaccination can give a false sense of security.

Another critical factor for vaccination is the number and timing of administration of vaccine doses. The number of doses depends on the vaccine and type of bird. There are insufficient studies on the duration of vaccine-induced immunity, which will vary with vaccine formulation, as well as with the overall health of the bird. In the laboratory, a single dose of vaccine in chickens at least 3 weeks of age without maternal antibody can provide adequate protection by 3 weeks post-vaccination (Swayne et al., 2000; Abbas et al., 2011; Kapczynski et al., 2013). However, in the field, there are reports of birds being vaccinating numerous times and still becoming clinically affected or dying when exposed to AIV (Naeem and Hussain, 1995; Kilany et al., 2010).

Vaccination of young birds might not work optimally, since birds are not fully immunologically mature until about 3 weeks of age and maternal antibodies can interfere with vaccination (Eidson et al., 1982; Maas et al., 2011; Faulkner et al., 2013). Vaccinating birds which are sick from other pathogens (particularly immunosuppressive agents) and/or poorly managed (e.g. inadequate nutrition, poor air quality, poor temperature control during brooding) will also affect the response to the vaccines and could necessitate more doses (Box et al., 1988; Hangalapura et al., 2003, 2004).

Coverage of the target population with adequate doses of vaccine must be achieved to develop 'herd (flock) immunity'. National vaccine coverage rates have been reported for some AIV outbreaks and have varied greatly (Swayne et al., 2011). A study of layer chickens in Vietnam used the basic reproduction number (R0) value of AIV to estimate that a perfect vaccine coverage should be at least 60%; however, the authors noted that no vaccine is perfect and a higher coverage is probably needed in the field (Bouma et al., 2008). On the basis of the proportion of chickens with HI antibody titers ≥16, Bouma et al. (2008) showed that adequate protection is achieved when the vaccine coverage is 90%.

The availability of vaccines can be a limiting factor. Vaccines against AIV are not routinely produced or even licensed in many countries. In areas where H5, H7 or H9 strains are common or endemic, vaccines for those subtypes may be available. However, in situations where vaccines are needed but not available, there will be a lag time of weeks to months before a vaccine can be produced and even more time for efficacy testing. In urgent cases, vaccines have been prepared and used without efficacy testing, e.g. LPAIV in turkeys in the USA in the 1980s and the H7N3 outbreak in Mexico in 2012. In the early 2000s, some countries developed stockpiles of H5 and H7 vaccines, but such stockpiles were not deemed to be cost effective and were not replaced after they had expired.

Future approach to vaccination against avian influenza

The use of vaccines against LPAIV and HPAIV throughout the world increased markedly after 2006, when H5N1 HPAIV spread from Asia into Africa and Europe (Swayne et al., 2011). Vaccination is considered by some farmers to be necessary for rearing chickens in regions where H5N1 HPAIV is endemic, i.e. Egypt, China, Indonesia and Vietnam. Prior to this, vaccination primarily had been used temporarily and locally as an adjunct to eradication programs. One exception has been Mexico, where vaccination for H5 AIV has been ongoing since 1994 (Escorcia et al., 2008). Recurrent introductions of AIV into domestic poultry in the Middle East will likely necessitate vaccination against H9N2 LPAIV to maintain poultry production.

In the USA, it is unlikely that vaccination against HPAIV would be implemented, whereas the use of vaccines against LPAIV is situation dependent. Similarly, although the European Union (EU) allows for emergency vaccination, current control measures rely mainly on the destruction of infected or potentially infected birds (EU directive 94/2005/CE). In both the USA and EU, comprehensive plans, including surveillance and an end date, are required to be in place before regulatory authorities will approve the use of vaccines against AIV.

A final element, which increasingly affects control of influenza in domestic animals, is concern for public health. Transmission of AIV from poultry to human beings has been documented on numerous occasions (Lin et al., 2000; Fouchier et al., 2004; Hirst et al., 2004; Chen et al., 2013; Bonfanti et al., 2014). This has raised concerns about a new pandemic virus, particularly if reassortment occurs between an avian virus and a human-adapted seasonal influenza virus. A current example where vaccination may be considered primarily for public health benefit is with H7N9 LPAIV in China.

Effective vaccination requires good quality vaccines and proper application (Table 2). Obstacles to successful vaccination programs include insufficient quantities of high quality vaccine, ability to maintain the cold chain and not enough skilled veterinary technicians to administer the vaccine (OFFLU, 2013). Many of these problems, such as having trained vaccinators, can be mitigated with adequate resources. Poor quality vaccines and inappropriate application (e.g. in birds which are too young) have led to vaccine failures in the field (Eidson et al., 1982; Naqi et al., 1983; Solano et al., 1986; Kim et al., 2010).

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Table 2
Factors affecting vaccine efficacy.

Factor	Notes
Maternal antibodies	Interfere with vaccine
Prior exposure to a vector agent (for vectored vaccines)	Immunity to the vector inhibits replication, diminishing response to the vaccine
Prior infection with immunosuppressive agents	The immune system of the animal does not mount a sufficient response
Antigenic match between the vaccine and field virus	Antibodies are not sufficiently matched to field virus for full protection
Antigen load and immunogenicity of the vaccine	A sufficient immune response is not induced
General health and condition of the animal (e.g. nutritional, genetic)	The immune system of the animal does not mount a sufficient response
Pathotype of field virus	Inactivated vaccines protect better against high pathogenicity avian influenza virus (HPAIV) than low pathogenicity avian influenza virus (LPAIV)
Vaccine coverage (i.e. percent of population vaccinated)	Enough animals must be protected to halt transmission
Species of bird	Vaccine should be formulated for the target species for optimal response
Duration of immunity	Exposure after immunity wanes could lead to infection and disease
Number of doses	Booster doses can improve immunity over time
Quality of administration	A full dose is optimal and requires proper equipment and training.
Speed of immunity development after vaccination	Exposure before immunity develops could lead to infection and disease

Conclusions

The utilization of AIV vaccines by different countries will continue to vary, since economics and industry structures are not uniform. There is no clear answer as to what is the optimal method to control AIV. Two disparate approaches have developed for using vaccines to control AIV; one is to eradicate AIV with no or very limited vaccination, which has been successful in the USA, Canada, Europe, Australia and Chile, while the other is to live with the virus in poultry, using vaccination to reduce production losses when the situation and infrastructure make eradication difficult. In the latter circumstance, vaccination can be used to reduce environmental levels of virus, which reduces the risk of human infection. Unfortunately, these infections often spill into previously uninfected areas. Permitting AIV to circulate in poultry also allows for reassortment events to occur and the possibility of new, possibly pandemic, viruses to arise, which affects both animal and public health. Currently, there is a need to develop vaccines with improved efficacy and potency which can be mass applied. Also, the goal of vaccination needs to be clearly defined and the success of a vaccination programme should be assessed against such goals. Lastly, but probably most importantly, biosecurity will be a critical component of any AIV prevention and control strategy, and should be maintained at a high level to complement vaccine use.

Conflict of interest statement

Neither of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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